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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/970,453	10/02/2001	Shulamit Eyal	20174C-002410US	9637
20350 7590 01/08/2008 TOWNSEND AND TOWNSEND AND CREW, LLP TWO EMBARCADERO CENTER EIGHTH FLOOR SAN FRANCISCO, CA 94111-3834			EXAMINER COOK, LISA V	
			ART UNIT 1641	PAPER NUMBER
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Office Action Summary**

Application No.

09/970,453

Applicant(s)

EYAL ET AL.

Examiner

Lisa V. Cook

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 05 October 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,3,4,7 and 10-13 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 3, 4, 7 and 10-13 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/05/07 has been entered.
2. Currently claims 1, 3-4, 7, and 10-13 are pending and under consideration. Claims 2, 5-6, 8-9 and 14-18 have been canceled at Applicants request.
3. Objections and/or rejections of record not reiterated below have been withdrawn.

## REJECTIONS MAINTAINED

### *Claim Rejections - 35 USC § 103*

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

I. Claims 1, 3, and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kopf-Sill et al. (US Patent #6,613,512) or Kopf-Sill et al. (US Patent #6,524,790) in view of Crabtree et al. (Analytical Chemistry, 1999, 71, 2130-2138).

Kopf-Sill et al. disclose methods and microfluidic devices to measure reactants and reaction products while considering velocity. See column 1 line 64 through column 2 line 23.

Reactants and products with different velocities (characteristics of an analyte) are measured in a microfluidic channel. See column 2 lines 36-37 and lines 57-58. In one embodiment the fluid samples are transported from a first position to a second position by electroosmotic flow (claim 4). See column 6 lines 15-18. The time dependent data generated is processed to include baseline subtraction and masking for accurate measurements of the analyte of interest (normalizing and considering velocity). See column 1 lines 64-67 and column 2 lines 18-42.

Multiple detection positions/zones are taught at two different time points in figure 1. See figure 1 - Time= $t_2$  and Time= $t_4$  (time difference measurement). The time difference and velocity are utilized in an equation to accurately measure the characteristic of interest in the analyte (claims 8 and 9). See column 5 line 11 through column 6 line 43. The various reactants and products can be assessed serially (individually) or simultaneously in the methods (claim 5). See column 2 lines 34-35. Kopf-Sill et al. teach the step of normalizing or eliminating the velocity component in reaction measurements. See column 5 lines 55-62 and column 8 lines 10-22.

Kopf-Sill et al. and Kopf-Sill et al. differ from the instant invention in not teaching sample detection at a plurality of detection zones between a first position (sample entry time) and a second position (sample end time).

However, Crabtree disclose a particle detection method, which converts multiple-point (Shah function) time dependent measurements into fluorescence frequencies allowing for the viewing of analyte speed (applicant's velocity). See abstract.

The SCOFIT (Shah convolution Fourier transform detection) principal is utilized in a system comprising multiple detection slits that detect the sample fluorescence at varied times ( $t=0$  through  $t=t_4$ ) during the flow of sample through a column or channel. For example, See figure 1 and page 2131. The particle is constantly interrogated (measured) at a number of evenly spaced points (slits or zones) along the column or channel simultaneously by a single detector and the signals measured from all of these points along the column are summed. See page 2131, 1<sup>st</sup> column, 3<sup>rd</sup> paragraph. This procedure advantageously isolated the analyte peak from interferences such as baseline drift and line noise. See abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use dual detection zones, slits, spaced zones (plurality of different detection zones) as taught by Crabtree et al. in either method of Kopf-Sill et al. (6,613,512 or 6,524,790) because Crabtree et al. taught that dual detection zones, slits, spaced zones advantageously isolated the analyte peak from interferences such as baseline drift and line noise. See abstract.

One of ordinary skill in the art would have been motivated to utilize dual detection zones (plurality of different detection zones) in order to more accurately detect the particles of interest.

**II.** Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kopf-Sill et al. (US Patent #6,613,512) or Kopf-Sill et al. (US Patent #6,524,790) in view of Crabtree et al. (Analytical Chemistry, 1999, 71, 2130-2138) as applied to claims 1, 3, and 4 above, and further in view of Squire et al. (Journal of Microscopy, 197(2) 2/2000, 136-149).

Please see Kopf-Sill et al. (US Patent #6,613,512) or Kopf-Sill et al. (US Patent #6,524,790) in view of Crabtree et al. as set forth above.

Kopf-Sill et al. (US Patent #6,613,512) or Kopf et al.-Sill (US Patent #6,524,790) in view of Crabtree et al. differ from the instant invention in failing to teach acousto-optic modulators.

However, Squire et al. teach methods for measuring fluorescence with wave acoustic-optic modulators placed in a series. This configuration analyzed multiple data sets simultaneously and distinctly. See abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use acoustic-optic modulators as taught by Squire et al. in either method of Kopf-Sill et al. (6,613,512 or 6,524,790) in view of Crabtree et al. because Squire et al. taught that "standing wave acoustic-optic modulators provide a means of modulating a continuous wave laser in a sinusoidal manner at high frequencies.

A number of these [lasers] can be employed in series to simultaneously modulate the excitation light of individual frequencies, their differences, and sums." See page 139 figure 2 and 2<sup>nd</sup> column last paragraph.

One of ordinary skill in the art would have been motivated to utilize these lasers in order to detect multiple frequencies simultaneously. There in evaluating several analytes.

**III.** Claims 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kopf-Sill et al. (US Patent #6,613,512) or Kopf-Sill et al. (US Patent #6,524,790) in view of Crabtree et al. (Analytical Chemistry, 1999, 71, 2130-2138) as applied to claims 1, 3, and 4 above, and further in view of Armstrong et al. (Cytometry, 40:102-108, 2/2000).

Please see Kopf-Sill et al. (US Patent #6,613,512) or Kopf-Sill et al. (US Patent #6,524,790) in view of Crabtree et al. as set forth above.

Kopf-Sill et al. (US Patent #6,613,512) or Kopf et al.-Sill (US Patent #6,524,790) in view of Crabtree et al. differ from the instant invention in failing to teach oligonucleotide detection including nucleotide measurements.

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However, Armstrong et al. teach this limitation. Their methods evaluate PCR probes that are linked to fluorescent molecules and measured by flow cytometry. See abstract. The method detects individual nucleotides from individual nucleotide fluorescence peaks. See figures 2, 3, and 4.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use detect oligonucleotides and the nucleotides which make up the oligonucleotides as taught by Armstrong et al. in either method of Kopf-Sill et al. (6,613,512 or 6,524,790) in view of Crabtree et al. because Armstrong et al. taught that genetic diversity is exhibited in disease and drug response and they can be effected by a single nucleotide difference/change/variant. See abstract.

### ***Response to Arguments***

5. Applicant contends that the combination of Kopf-Sill (US Patent #6,613,512) or Kopf-Sill et al. (US Patent #6,524,790) in view of Crabtree et al. does not make the instant invention obvious. Specifically, Applicant argues that the patents to Kopf-Sill et al. teach an analysis of a signal at a single detection zone and the use of that data to solely determine the rate or extent of an assay reaction. This argument was carefully considered but not found persuasive because Kopf-Sill et al. teach procedures that detect the sample at multiple periods within a single detection zone. For example, see US Patent #6,613,512 column 22 lines 1-5 and US Patent #6,524,790 column 29 line 29 through column 30.



Although Kopf-Sill et al. teach multiple measurements within a single zone (a single viewing region with various time points) the same multiple analysis can be achieved with the analysis of the analyte at multiple detection zones (or slits at various time points). In other words, the cited references and the instant invention are drawn to methods that measure the analyte at multiple time periods. It has been held that to be entitled to weight in method claims, the recited structure limitations therein must affect the method in a manipulative sense, and not to amount to the mere claiming of a use of a particular structure.

In order to make this obvious the reference to Crabtree et al. was added to the rejection under 35 USC 103(a). Crabtree et al. taught that dual detection zones, slits, spaced zones advantageously isolated the analyte peak from interferences such as baseline drift and line noise. See abstract. One of ordinary skill in the art would have been motivated to utilize dual detection zones (plurality of different detection zones) in order to more accurately detect the particles of interest. It has been held that the provision of adjustability, where needed, involves only routine skill in the art. In re Stevens, 101 USPQ 284 (CCPA 1954).

With respect to Kopf-Sill et al. merely measuring an assay reaction and not addressing the elimination of the velocity dependence measurement it is noted that velocity consideration is taught at column 2 lines 9-23, column 5 lines 11-30, and column 9-11 of US Patent #6,613,512 and at column 38 Example 1.

Also, the test for obviousness is not whether the features of one reference may be bodily incorporated into the other to produce the claimed subject matter but simply what the combination of references makes obvious to one of ordinary skill in the pertinent art. See In re Bent, 52 CCPA 850, 144 USPQ 28 (1964); In re Nievelt, 179 USPQ 224 (CCPA 1973).

Applicant contends that Crabtree et al. teaches a form of Fourier transform analysis that is exclusive for resolving multiple peaks in electrophoresis systems and does not relate to velocity measurements. This argument was carefully considered but not found persuasive because Crabtree et al. disclose that their “detection principal is applicable to a variety of separation-detection scenarios”. See page 2131 column 2 – 2<sup>nd</sup> paragraph. Further, in the specification it is disclosed that Crabtree et al. teaches Shah convolution transform to measure velocity in microfluidic devices. See specification page 2 lines 30-32.

Crabtree et al. teach the use of multiple measurements along the column of sample flow. The fluorescence measurements are combined and employed to measure the analyte and its mobility. See page 2131, 1<sup>st</sup> column, 3<sup>rd</sup> paragraph. This procedure advantageously isolated the analyte peak from interferences such as baseline drift and line noise. See abstract.

With respect to the advantages taught by Crabtree et al. disclosing that “[r]esolution is somewhat inferior to that seen in single point detection.....”, it is noted that this statement goes on to further indicate that improved chip design, mathematical, and instrumentation optimization will lead to performances superior to that of single-point detection. Please see abstract. A reference is not limited to its working examples, but must be evaluated for what it teaches those of ordinary skill in the art. *In re Chapman*, 357 F.2d 418, 148 USPQ 711 (CCPA 1966).

Applicant contends that Kopf-Sill does not teach multiple detection zones while Crabtree does not teach velocity elimination. This argument was carefully considered but not found persuasive because a reference is not overcome by pointing out that a reference lacks a teaching for which other references are relied. *In re Lyons*, 364 F.2d 1005, 150 USPQ 741, 746 (CCPA 1966).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant further, contends that there is no explanation within the references and no explanation by the Office as to how Kopf-Sill and Crabtree could be combined to yield Applicant's claimed method. This argument was carefully considered but not found persuasive because the office action recites that it would have been obvious to one of ordinary skill in the art at the time the invention was made to use dual detection zones, slits, spaced zones (plurality of different detection zones) as taught by Crabtree et al. in either method of Kopf-Sill et al. (6,613,512 or 6,524,790) because Crabtree et al. taught that dual detection zones, slits, spaced zones advantageously isolated the analyte peak from interferences such as baseline drift and line noise. See abstract. An obvious rejection is proper so long as the prior art suggests a reason or provides motivation to make the claimed invention, even where the reason or motivation is different from that discovered by applicant. *In re Dillon*, 919 F.2d 688, 696, 16 USPQ 2d 1897, 1904, (Fed. Cir. 1990) (in banc), cert. denied, 111 S. Ct. 1682 (1991).

Also, KSR forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*,-- USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007)(citing KSR, 82 USPQ2d at 1396).

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With respect to the rejections under 35 USC 103(a), including Squire et al. (Journal of Microscopy, 197(2) 2/2000, 136-149) and Armstrong et al. (Cytometry, 40:102-108, 2/2000), applicant contends that the additional references do not cure the deficiencies of Kopf-Sill or Kopf-Sill et al. in view of Crabtree et al. The rejection over Kopf-Sill or Kopf-Sill et al. in view of Crabtree et al. has been addressed above. Therefore the rejections are maintained.

6. For reasons aforementioned, no claims are allowed.

7. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The Group 1641 – Central Fax number is (571) 273-8300, which is able to receive transmissions 24 hours/day, 7 days/week. In the event Applicant would like to fax an unofficial communication, the Examiner should be contacted for the appropriate Right Fax number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

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you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, appearing to read 'Lisa V. Cook', with a stylized flourish at the end.

*Lisa V. Cook*

*Patent Examiner*

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*Remsen 3C-59*

*(571) 272-0816*